EIP Bulletin

TENNESSEE EMERGING INFECTIONS PROGRAM

Tennessee Department of Health Communicable and Environmental Disease Services — February 2006

Encephalitis in Tennessee: Etiologies & Enigmas

Encephalitis, or infection of the brain, results in 19,000 hospitalizations (7.3 hospitalizations per 100,000 population), 230,000 hospital days, and 1,400 deaths annually in the United States[1]. Despite the relative frequency of this diagnosis, encephalitis remains an enigmatic syndrome, with no causative infectious agent found in as many as 70% of cases[2]. Failure to rapidly identify pathogens causing encephalitis limits the ability of physicians to provide treatment to individual patients, and may impede community-wide interventions such as mosquito control. While more than 100 different infectious agents have been associated with encephalitis, the following represent organisms important to consider among Tennessee residents hospitalized with encephalitis (**Table 1**).

Herpes Simplex virus (HSV): HSV accounts for 10-20% of cases of encephalitis, and remains the leading cause of sporadic (as opposed to epidemic) encephalitis in the United States. Infection is typically caused by HSV-1, the virus associated with cold sores or fever blisters, although <15% of patients with HSE have orolabial lesions at the onset of neurological symptoms. HSV-1 has a predilection for infection of one or both temporal lobes, with clinical findings including fever, altered mental status, and temporal lobe seizures. Temporal lobe enhancement is typically present on brain MRI, although it may be absent early in the course of the infection.

Early administration of acyclovir significantly decreases the morbidity and mortality associated with herpes simplex encephalitis (HSE). For this reason, empiric acyclovir should be considered for all patients with encephalitis pending the results of diagnostic testing. Polymerase chain reaction (PCR) of cerebrospinal fluid (CSF) has a sensitivity and specificity of >95%, and has replaced brain biopsy as the diagnostic procedure of choice for HSE. This test is widely available through commercial

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Mosquito Diversity at an Enzootic EEE Focus in Western Tennessee

Eastern equine encephalitis (EEE) is caused by EEE virus which is transmitted by mosquitoes throughout the Americas. In North America, the distribution of EEE virus coincides with its enzootic vector, *Culiseta melanura*, principally along the Atlantic and Gulf coasts. EEE virus circulates in swampy coastal areas where *Culiseta melanura* feeds on wild birds. Inland foci have also been documented in the states of New York, Wisconsin, Michigan, South Dakota, Minnesota, Ohio and Tennessee. Humans and horses are affected when EEE "spills over" from swamp habitats through bridge vectors that feed on both birds and mammals.

Outbreaks of human disease in the United States are usually small, but have severe consequences including seizures, coma, and death. The case-fatality rate ranges from 35-90% and survivors often have persistent neurological deficits. Equine epizootics, with case-fatality rates approaching 90%, serve as sentinels for increased risk to humans from EEE virus. In Tennessee, equine epizootics occur periodically across the state (**Figure 1**). The Tennessee Department of Health (TDH) conducts surveillance for EEE by monitoring equine epizootics in collaboration with the Tennessee Department of Agriculture (TDA).

In September of 2005, in response to a laboratory-confirmed EEE equine epizootic, TDH, TDA, and the UT Agricultural Extension Service conducted an epidemiologic investigation in Henderson, Madison, and Chester counties. The investigation was conducted on September 21st and 22nd and included active case finding, site visits and mapping of affected farms, serologic screening of horses, and mosquito trapping.

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laboratories. Early in the course of infection, the PCR may be falsely negative[3]; therefore, if a high clinical suspicion exists, acyclovir therapy should be extended for a complete therapeutic course of 14-21 days.

West Nile virus (WNV): Human WNV infection has been reported in Tennessee since 2002, with the majority of cases presenting with meningoencephalitis. Neurological involvement is most common among immunocompromised patients and healthy adults older than 60 years of age. The incidence in Tennessee typically peaks in late August and September, correlating with periods of maximal mosquito populations. Clinical findings are nonspecific, and may include fever, headache, altered mental status, and weakness. Acute flaccid paralysis of one or more limbs is increasingly reported as a manifestation of WNV. Neuroimaging is nonspecific, but may show thalamic involvement in a subset of cases.

Laboratory diagnosis is complicated by cross-reactivity between WNV and other flaviviruses. Demonstration of WNV IgM antibody in CSF is considered diagnostic of acute infection. While elevated serum antibodies to WNV are suggestive of the diagnosis, IgM may remain detectable for more than 500 days following acute infection. There is no specific antiviral therapy for West Nile virus encephalitis, and the mainstay of therapy is supportive care.

La Crosse (LAC) virus: La Crosse virus is a mosquito-borne pathogen, with infections most commonly reported among patients in the eastern part of the state. Cases occur throughout the spring, summer, and fall months. Unlike WNV, where symptomatic infections are more common in older adults, LAC virus meningoencephalitis occurs almost exclusively in children. Seizures are common, and the CSF typically shows a lymphocytic predominance.

LAC virus infection may be diagnosed by serology. At the time of presentation, many patients will have IgM antibody present in the serum. Occasionally, patients may be seronegative at onset of neurological symptoms, but develop antibody over the ensuing weeks. Convalescent serum should be obtained if there is a clinical concern for LAC virus infection. Anecdotal reports suggest ribavirin may be beneficial in severe cases, but standard therapy remains supportive care. Patients with LAC virus encephalitis typically make full recoveries.

Table 1. Selected Causes of Encephalitis Among Tennessee Residents

Organism	Epidemiology	Diagnostic Testing	Treatment	Reportable in Tennessee*
Herpes simplex virus	Year-round, all ages	CSF PCR	Acyclovir	No
West Nile virus	Summer and fall, primarily adults	CSF or serum IgM antibodies	Supportive care	Yes, Category 1
La Crosse virus	Spring through fall, primarily children	Serum IgM or IgG antibodies	Supportive care	Yes, Category 1
Rickettsia rickettsii or Ehrlicihia chaffeensis	Spring through fall, all ages	4-fold rise in IgG antibody titer, whole blood PCR for *Ehrlichia*	Doxycycline	Yes, Category 2
Rabies	Year-round, all ages	Biopsy of nape of neck, antibody in serum & CSF/saliva PCR	None (Prophylaxis of contacts)	Yes, Category 1

*Category 1 infections require immediate telephone reporting to the health department, followed by a written report on the PH-1600 form. Category 2 infections require only the written report on the PH-1600 form.

Ehrlichia chaffeensis & Rickettsia rickettsii: These bacteria, the causative agents of human monocytic ehrlichiosis (HME) and Rocky Mountain spotted fever (RMSF) respectively, are tick-borne pathogens that cause neurological manifestations in about 20% of infections. Incidence peaks during spring, summer, and fall months, with most patients recalling a tick attachment or recent outdoor activities placing them in tick habitat. Clinical findings include fever, altered mental status, meningismus, and seizures. A rash is noted in 85% of cases of RMSF, although may develop late in the course of the illness. Skin findings are evident in only 30% of patients with HME. Both agents are variably associated with leukopenia, thrombocytopenia, and elevated liver enzymes.

Doxycycline is the drug of choice for both of these infections. Although penetration into the CSF is marginal, multiple reports suggest doxycycline is efficacious in treatment of patients with CNS symptoms. Demonstration of elevated antibodies to either *E. chaffeensis* or *R. rickettsii* is diagnostic, but patients are usually seronegative at the time of presentation, necessitating serologic testing of convalescent serum obtained 2-4 weeks after illness onset. PCR of whole blood for *Ehrlichia* species allows rapid diagnosis of this infection, but is insensitive and not readily available for *R. rickettsii*.

Rabies virus: Rabies is an almost uniformly fatal, although preventable, cause of encephalitis contracted through contact with an infected animal. Rabies in animals remains a significant public health problem, with 46 cases of zoonotic rabies confirmed in Tennessee during 2005. In contrast, only 1-2 human cases of rabies are reported nationally each year, with the last case in Tennessee identified in 2002. While bats are the most common vector for human rabies, the majority of patients infected with bat-associated strains lack a documented antecedent bite. Symptoms of rabies include paresthesias at the site of inoculation followed by anxiety, hallucinations, hydrophobia, autonomic instability, and coma.

Prophylaxis with rabies immunoglobulin and vaccine is protective if given at the time of exposure, however once neurological symptoms develop there is no effective therapy. However, early diagnosis of rabies is important for prognosis and to identify family members and health care workers requiring prophylaxis. Diagnostic studies include nuchal biopsy for direct fluorescent antibody testing, salvia for rabies PCR, and serologic testing of serum and CSF. These tests are variably positive at the time of presentation, necessitating multiple testing modalities and sequential testing if a high clinical suspicion persists.

Additional pathogens and resources: The above agents represent a subset of causes of encephalitis among residents of Tennessee. Barriers to diagnosis of an infectious agent include inability to culture viruses and fastidious bacteria from the CSF, the need

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Decline in Invasive Pneumococcal Disease Among Young Infants and Elimination of Racial Disparity in Disease Rates

Streptococcus pneumoniae causes invasive diseases such as meningitis, bacteremia and pneumonia in children.[1] A heptavalent pneumococcal conjugate vaccine (PCV7) was licensed in February 2000 and was recommended for all children 2 through 23 months of age in the United States. Since PCV7 introduction, the rate of invasive pneumococcal disease among U.S. children younger than 2 years has decreased by at least 60%. Concurrently, rates of invasive pneumococcal disease in adults have decreased.[2] These declines suggest that PCV7 vaccination of children 2-23 months of age has led to changes in pneumococcal carriage in both the target and non-target populations.

Neonates (0 to 30 days) and young infants (31 to 90 days) are at high risk for certain bacterial infections, most often due to group B *Streptococcus*, *E. coli* and *Listeria monocytogenes*. Although *Streptococcus pneumoniae* causes invasive disease, the incidence has not been clearly defined. Clinical manifestations of *S. pneumoniae* infections in neonates and young infants are serious and include meningitis, sepsis, bacteremia, pneumonia, otitis media, abscesses, and bone and joint infections. Whether PCV7 vaccination of children 2 months of age and older would protect neonates and young infants by changing pneumococcal carriage in those too young to receive PCV7 is unknown. Active Bacterial Core Surveillance (ABCs) staff sought to determine the rates of invasive pneumococcal diseases among neonates and young infants in eight states performing active, population-based laboratory surveillance (including 11 counties in Tennessee) and to compare the rates before and after the introduction of PCV7 in 2000.

A total of 170 cases of invasive pneumococcal disease (IPD) were identified among infants 0 to 90 days of life from July 1997 through June 2004. Twenty-four cases were identified during the transition year; they are shown in graphs but are not included in any analyses. The remaining 146 cases occurred during the three pre-PCV7 years and three post-PCV7 years and comprised the study population. The median age of onset of infection was 46 days (range 0 to 88 days). The age group, racial distribution, gender and state from which IPD cases were identified were statistically similar during the two periods; however, the proportion that was black in the post-PCV7 years was half that of the pre-PCV7 years. The annual number of IPD cases during the pre-PCV7 years ranged from 26 to 35 and from 14 to 24 during the post-PCV7 years. Isolated bacteremia accounted for 94 (64%) IPD cases, while pneumonia was noted in 27 infants (18%), meningitis in 22 (15%) and septic arthritis and/or osteomyelitis in 3 (2%).

Figure 1. Rates of invasive pneumococcal disease (IPD) by age group and year.

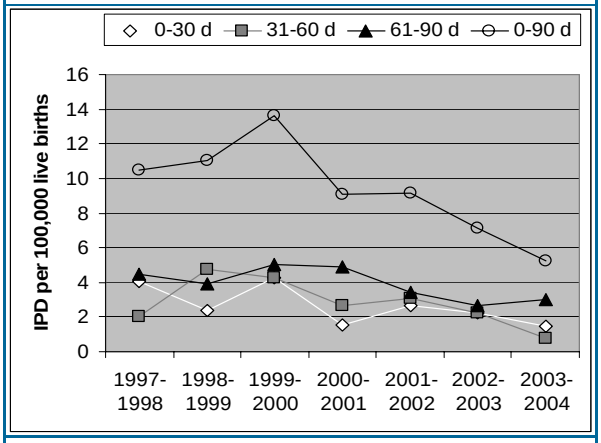
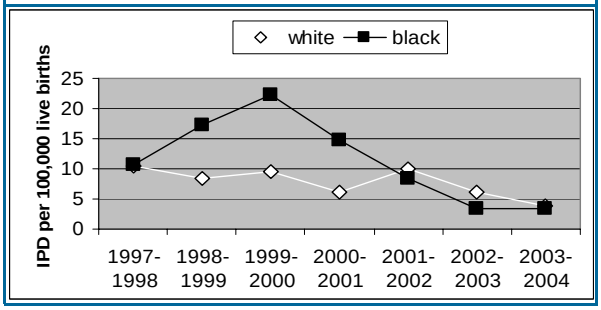


Figure 2. Rates of invasive pneumococcal disease for children 0 to 90 days of age by race and year.



The eight surveillance areas had 759,739 live births during the three pre-PCV7 years and 794,106 live births during the three post-PCV7 years, an average of 258,974 live births per year. Among all the infants 0 to 90 days of age, the average rate of IPD decreased significantly from 11.8 (95% C.I. 9.6 to 14.5) in the pre-PCV7 years to 7.2 per 100,000 live births (95% C.I. 5.6 to 9.4) in the post-PCV7 years (**Figure 1**). The average rate of IPD decreased by 39%, 45% and 32% for infants 0 to 30, 31 to 60 and 61 to 90 days of age, respectively. Notably, the rate of IPD among infants 0 to 60 days of age decreased from 7.3 (95% C.I. 5.6 to 9.5) pre-PCV7 to 4.2 per 100,000 live births (95% C.I. 3.0 to 5.9) post-PCV7, although PCV7 is not recommended until infants reach 2 months of age.

Among black infants, IPD rates declined significantly from 17.1 (95% C.I. 11.9 to 24.6) during the pre-PCV7 years to 5.3 per 100,000 live births (95% C.I. 2.8 to 10.1) during the post-PCV7 years (**Figure 2**). Among white infants, IPD rates declined from 9.6 (95% C.I. 7.3 to 12.7) to 6.8 per 100,000 live births (95% C.I. 4.9 to 9.4). Hence, the racial disparity in IPD rates for black and white infants in the pre-PCV7 years was eliminated in the post-PCV7 years.

Among infants 0 to 90 days of life, IPD rates decreased significantly after PCV7 introduction. The change was attributable to a decline in the rate of disease caused by PCV7 serotypes. The 42% decline in IPD rates among infants 0 to 60 days old is similar to declines reported for children older than 5 years of age and adults, who are not specific targets of PCV vaccination recommendations. These data suggest that neonates and infants too young to receive PCV7 are benefiting from herd immunity. "Herd immunity" occurs when vaccinated persons in a population indirectly protect unvaccinated population members by impeding the transmission of the infectious agent in the population.

The benefit of PCV7 is evident well beyond the young children who routinely receive this vaccine. This relatively new vaccine has been tremendously popular with physicians of young children but has produced tangible benefits in both adults and younger infants.

[1] Advisory Committee on Immunization Practices. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2000;49(RR-9):1-35.

[2] Whitney CG, Farley MM, Hadler J et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003;348:1737-46.

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to obtain convalescent serum, limited volume of CSF for testing at multiple laboratories, and limited access to PCR testing (with the exception of HSV) through commercial laboratories.

The Tennessee Unexplained Encephalitis Surveillance (TUES) Study, a sub-project of the Tennessee Emerging Infections Project, was begun in January 2000 to perform enhanced diagnostic testing for encephalitis. Tennessee joins California and New York as the 3rd EIP site to perform comprehensive testing for infectious causes of encephalitis, with the goal of learning more about the epidemiology, clinical manifestations, and outcomes in encephalitis.

For questions about the TUES study, or to refer a patient with encephalitis into the study, please contact the study coordinators at 615-322-1519 or toll-free at 1-877-756-5800.

[1] Khetsuriani N, Holman RC, Anderson LJ. Burden of encephalitis-associated hospitalizations in the United States, 1988-1997. Clin Infect Dis 2002;35(2):175-82. [2] Eron LJ, Lipsky BA, Low DE, et al. Managing skin and soft tissue infections: expert panel recommendations on key decision points. J Antimicrob Chemother. 2003;52(Suppl 1:13-17).

[2] Glaser CA, Gilliam S, Schnurr D, et al. In search of encephalitis etiologies: diagnostic challenges in the California Encephalitis Project, 1998-2000. Clin Infect Dis 2003;36(6):731-42.

[3] Weil A, Glaser C, Amad Z, Forghani B. Patients with suspected herpes simplex encephalitis: Rethinking an initial negative polymerase chain reaction result. Clin Infect Dis 2002;34:1154-7.

Mosquito Diversity at an Enzootic EEE Focus (continued)

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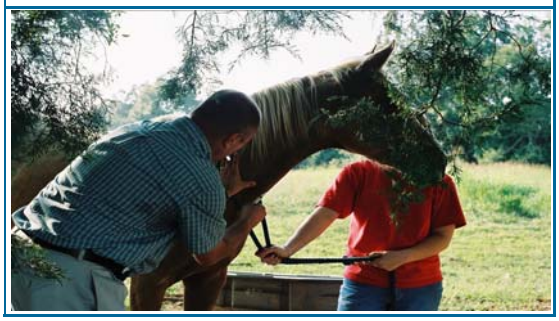
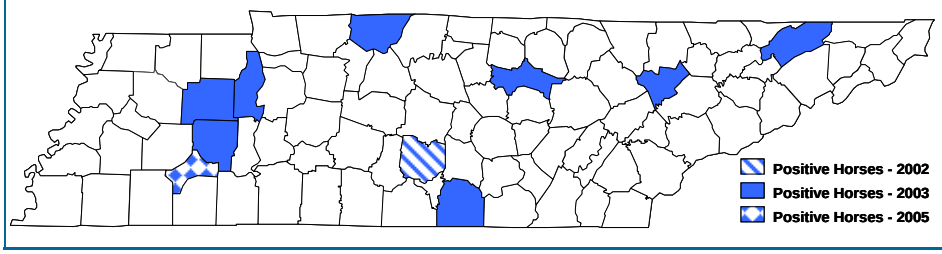
One laboratory-confirmed equine EEE case, which died on September 6th, and least 6 other horse fatalities were identified on 5 farms. All 6 unconfirmed horses had symptoms consistent with EEE infection, were unvaccinated, and died between September 2nd and 20th. The five farms were geo-coded and mapped to evaluate spatial relationships and landscape features. All 6 unconfirmed equine cases occurred within a 3-mile radius of the laboratory-confirmed equine case. All cases were located near a prominent hardwood swamp habitat. Blood samples were taken (**Figure 2**) from other horses residing on the farms where the confirmed and unconfirmed cases occurred. Results of EEE IgM capture ELISA were typical of recent EEE virus infection in 1 (10%) of 10 horses tested. For mosquito trapping, CO2-baited CDC light traps and gravid traps were placed at the 5 farms. Each trap site was geo-coded and mapped. Mosquito trapping was performed during two consecutive nights. Trapping was also done within the hardwood swamp habitat. Various mosquito species from each collection site were trapped. Mosquitoes will be identified to species and tested for EEE virus.

Figure 2. Collection of blood from horses at confirmed and suspect EEE case sites for antibody testing.



EEE virus is extremely dangerous to horses and people. Additionally, it is considered to be a potential bioterrorism agent. During this investigation, TDH, TDA, and the UT Agricultural Extension Service collaborated to describe the epizootic and assess risks to the public. A press release issued by TDA reminded horse owners to vaccinate their horses and included information from TDH on preventive measures for the public to protect themselves against mosquitoes. Additional surveillance and investigation are planned for 2006 at this enzootic EEE focus.

Figure 1. Distribution of EEE horse cases in Tennessee from 2002 to 2005.



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